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Short running headline: Intubation and asthma

**Predicting the Requiring Intubation and Invasive Mechanical Ventilation among
Asthmatic Exacerbation-related Hospitalizations**

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Abstract

Objective: To identify the predictors of requiring intubation and invasive mechanical ventilation (IMV) in asthmatic exacerbation (AE)-related hospitalizations.

Methods: This study was conducted in southern Thailand between October 2016 and September 2018. The characteristics and clinical findings of patients admitted for AE requiring intubation and IMV were analyzed. The variables were evaluated by univariate and multivariate analysis to identify the independent predictors.

Results: A total of 509 patients with a median age of 53 years were included in the study. Being female (60.2%), having no previous use of a controller (64.5%), having a history of smoking, and having a high level of white blood cell count ($14,820 \text{ cells/mm}^3$) were the significantly more common characteristics of the patients requiring mechanical ventilation. Univariate analysis showed that being male (OR=1.96 95%CI, 1.22-3.13), having a history of 1-2 AEs in the past 12 months (OR=3.27 95%CI, 1.75-6.12), and having an absolute eosinophil count $\geq 300 \text{ cells/mm}^3$ (OR=1.68 95%CI, 1.05-2.69) were associated with patients requiring IMV, whereas the patients who were taking a reliever (OR=0.36 95%CI, 0.23-0.57) and controller (OR=0.42 95%CI, 0.27-

0.68) were associated with a decreased risk of requiring intubation and IMV. In multivariate analysis, only 1-2 AEs within the past 12 months (OR=3.12, 95%CI:1.19-8.21) was an independent predictor of requiring intubation and IMV in patients with AE-related hospitalization (p=0.021).

Conclusions: This study found that a history of 1-2 asthmatic exacerbations in the past 12 months was a strong independent predictor for the requirement of intubation and IMV in patients hospitalized for AE-related conditions.

Keywords: asthma, invasive mechanical ventilation, asthmatic exacerbation, hospitalization, respiratory failure

Introduction

Asthma is a highly prevalent disease affecting more than 239 million people worldwide (1). Even though asthma guidelines are updated yearly and highlight the importance of using preventative therapies to reduce the risk and frequency of asthmatic exacerbation (AE) (2, 3), the exacerbation rates for patients with asthma in real-world settings remain high (4). Therefore, this complication is still the main unresolved problem in health care systems in terms of substantial morbidity, occasional mortality and considerable medical and economic costs (5, 6). Clinical features which have a demonstrated close association with the exacerbation of asthma include a progressive increase in the symptoms of shortness of breath, coughing, wheezing or chest tightness as well as a progressive decrease in lung function (2). Studies conducted in the Thai setting have shown an increasing trend in the number of asthma exacerbations (7, 8) despite numerous updates of the guidelines and advances in the medications. Clinical experience shows that 20% of asthmatic patients have had exacerbations requiring either treatment in the emergency department or hospitalization (9), while 25% of the asthmatic patients discharged

from hospital were readmitted (10). The clinical risk factors for AE include uncontrolled asthma symptoms (11-13), high short-acting Beta-2 agonist (SABA) use (14), inadequate inhaled corticosteroid, poor adherence to medications (15), incorrect inhaler technique (16), comorbidities (17), exposure to smoking and/or allergens (18), low lung function (18), history of intubation (19), or ≥ 1 severe exacerbation in the past 12 months (20). An estimated 36% of asthma-related emergency patients required admission (7), while older age and female gender were demonstrated as factors associated with hospital admission for acute asthma (21, 22). In addition to blood eosinophil, there was also a discrepancy between levels of blood eosinophil and exacerbation rates. However, a recent meta-analysis demonstrated that a high level of blood eosinophils is related to more frequent asthma exacerbations (23).

In cases of life-threatening exacerbation, those requiring intubation and IMV have been shown to have a higher asthma-related death rate (24), higher economic costs, and worse clinical outcomes (25). Although a limited number of studies have extensively reviewed the clinical characteristics of near-fatal asthma (26, 27), little is known about the risk factors for requiring intubation and IMV in AE-related hospitalizations, while possible differences in the risk factors among different populations have not been examined. Therefore, this study aims to evaluate the characteristics and identify the independent clinical predictors of requiring intubation and IMV in patients with AE-related hospitalizations.

Methods and materials

Study design

This was a retrospective cohort design study conducted between October 2016 and September 2018 in a university-affiliated tertiary care center at Hatyai Regional Hospital, Thailand. The protocol was approved by the institutional review board of Hatyai Regional

Hospital (approval number 65/2562) and also registered at ClinicalTrials.gov, number NCT04277078. The study was based on medical charts of inpatient in which the diagnosis was AE as defined by the International Statistical Classification of Diseases and Related Health Problems 10 (ICD-10) codes J45.0-J45.9 and J46 in the discharge summary. All admission charts were externally audited and the diagnoses of AE resulting in hospitalization were confirmed by a pulmonologist. For patients with multiple visits for AE beyond the index event, the first event was incorporated into the analysis.

Patients

The study population consisted of patients who met the criteria of being diagnosed with asthma and AE as defined according to the standards of the Global Initiative for Asthma (GINA) (2) and of being aged > 15 years. Patients who were pregnant or who had a history of lung cancer, tuberculosis, lung fibrosis or previous lung surgery were excluded.

Data collection

The demographic and clinical data associated with the investigation and treatment of each admission were extracted from medical records. Data including age, gender, smoking status, follow-up clinic, comorbidities, number of AEs with or without hospitalization in the past 12 months, and current medications being taken were recorded. The GINA step classification of patients was performed by physicians. Clinical parameters including initial body temperature (BT), systolic blood pressure, diastolic blood pressure, pulse rate (PR), respiratory rate (RR), the presence of respiratory failure requiring intubation and IMV, white blood cell (WBC) count, absolute neutrophil count (ANC), and absolute eosinophil count (AEC) were collected. Data on

clinical outcomes including complications, length of hospital stay, death, and dose of systemic steroids (prednisolone equivalent dose (PED)) were also collected.

Statistical analysis

All statistical analyses were conducted using SPSS Statistics version 23 for Windows. Patient demographic data, admission details and hospital characteristics were summarized in frequency tables under patients who required intubation and those who did not. Categorical values, expressed as numbers with proportions, were analyzed using the Chi-squared test. Continuous or ordinal values were summarized as median values with an interquartile range, and were analyzed by non-parametric Mann-Whitney U test. Stepwise multivariable logistic regression was conducted to determine the significant clinical predictors for patients requiring intubation and IMV. All factors with a univariate p -value <0.1 were considered candidates in multivariate regression analysis. Two-sided p -values <0.05 were considered significant.

Results

A total of 509 patients were identified as having a principal diagnosis of AE (Table 1). Of these, the median age was 53 (40, 65) years and 72.1% were female. Additionally, 48.1% of the patients were non-smokers, which means that 65.2% of the patients had data available regarding smoking. The median pack-years of smoking was 10 (3.2, 23.3). Of the 509 patients, 29.3% had never had regular follow ups and 47.3% were not currently taking controllers. Most of the patients had either none (52.1%) or one or two (36.9%) of the prespecified coexisting conditions, most commonly diabetes (15.7%), cardiovascular disease (10%), allergic rhinitis (9.6%), and gastroesophageal reflux disease (4.1%). In addition, 55.4% of the patients had had at least one

AE in the past 12 months, with a median number of 1 occurrence (0, 3). Intubation with IMV was required by 93 of the 509 patients (18.3%).

Table 2 compares the characteristics and clinically relevant data of the intubated and the non-intubated patients. In the intubation group, there was a greater ratio of males, patients not using a controller and active smokers than in the non-intubation group. According to GINA classification, 64.5% of the intubated patients were undergoing GINA step 1 treatment, which was significantly higher than for the non-intubated patients (43.3%). In addition, the patients requiring intubation and IMV had significantly higher BT, PR, RR, WBC and ANC compared with the other group. Table 3 shows the hospitalization outcomes. Thirteen of the 93 patients in the intubation group died during hospitalization, while there were no deaths in the non-intubation group. The intubated patients also had a significantly longer length of stay (4 vs 2 days) and greater occurrences of shock (19 of 93 patients vs 0 of 416 patients) and pneumonia (20 of 93 patients vs 12 of 416 patients) than the non-intubation group. The median amount of total systemic steroid use during hospitalization among the intubated patients (175 mg of PED) was significantly higher than among the non-intubated patients (87.5 mg of PED). The univariate analysis results for determining the possible clinical predictors of requiring intubation and IMV in AE-related hospitalizations are shown in Table 4. Univariate analysis revealed that being male OR=1.96 [95%CI, 1.22-3.13]; having a history of 1-2 AEs in the last 12 months, OR=3.27 [95%CI, 1.75-6.12]; and having a level of AEC ≥ 300 cell/mm³, OR=1.68 [95%CI, 1.05-2.69] were associated with requiring intubation and IMV, while reliever use, OR=0.36 [95%CI, 0.23-0.57] and controller use, OR=0.42 [95%CI, 0.27-0.68] were inversely clinical predictors of requiring intubation and IMV. Multivariable logistic regression analysis showed that only 1-2

AEs in the last 12 months (OR=3.12, 95%CI:1.19-8.21) was independently associated with the risk of requiring intubation and IMV in hospitalized AE patients ($p=0.021$)

Discussion

The current study identified independent predictors of requiring intubation and IMV in patients hospitalized for AE-related conditions. After adjusting the variables, a history of 1-2 AEs in the past 12 months was the only significant clinical predictor for these adverse events. Overall, 18.3% of hospitalized patients with AE required intubation and IMV, while there was a mortality rate of just 2.6%. In addition, it was found that those with intubation were significantly more likely to be male, to have fewer comorbidities, to be active smokers, to have not previously used controller medications, and to be classified as receiving GINA step 1 treatment. A significantly higher level of blood neutrophil was observed in the intubated patients, while the overall clinical outcomes including length of hospital stay, death rate and pneumonia were also higher in those patients.

In our study, the majority of the patients hospitalized for asthma-related conditions was female. The relationship between gender and the underlying mechanisms of asthma has previously been studied (28). The sex hormones, estrogen and progesterone, are potentially important mediators establishing allergic inflammation by inducing eosinophils to infiltrate the airways, increasing serum IgE concentrations, and enhancing interleukin-13 protein expression in the lungs (29), which could explain the predominance of females experiencing AE in our study. The paradoxical finding that a higher proportion of patients requiring mechanical ventilation were classified in GINA step 1, the mildest of the GINA steps, may be explained by the fact that they did not receive the proper controller medication, and not because they indeed had a mild form of asthma. Although the previous study demonstrated the blood neutrophil

counts associated with a risk of moderate exacerbation in asthma patients (31), this variable has not reached statistical significance as a clinical predictor of intubation. AEs are usually related to respiratory infections and their severity, which seem more likely to be the cause of a high blood neutrophil count. Furthermore, smoking may enhance inflammation associated with a high blood neutrophil count. In asthmatic smokers, the mechanism of corticosteroid resistance is a result of alterations in airway inflammatory cell phenotypes (32), which may lead to a poorer response to anti-inflammatory agents. Moreover, not using a controller, having no previous asthma diagnosis, or having uncontrolled asthma might be reasons for using a high dose of systemic steroids in patients with intubation. We conclude that requiring intubation and IMV in AE undoubtedly resulted in longer hospital stays, higher complication rates including shock and pneumonia, and higher mortality. A mortality rate of 2.6% was found for patients admitted to the hospital due to AE (33). However, for patients with near fatal asthma episodes, this rate increased to 3.1% (26).

A recent study demonstrated how previous exacerbation was associated with a higher risk of repeat exacerbations (10). To our study, this factor has been evidenced as a significant clinical predictor for requiring intubation and IMV. There are many reasons explaining this finding. Firstly, the majority of intubated patients were in step-1 GINA, meaning that they may not have been taking any controller or had never previously been diagnosed with asthma, resulting in airway inflammation and poorly controlled symptoms, increasing the risk of exacerbation. Secondly, although blood eosinophils have not been demonstrated as a predictive factor for requiring intubation and IMV, a high level of blood eosinophils is associated with worsening airway inflammation leading to frequent exacerbations (23, 34) and has been identified as increasing the risk of exacerbation in patients who smoke(35). Thirdly, smoking is a

main precipitating factor in asthmatic smokers and increases the risk of frequent exacerbations. Therefore, we believe that if clinicians have a concern over the factors causing AE, this problem should be resolved.

The SABA is considered the frontline defense for acute asthma symptoms (36), and using this medication in the treatment of AE produces the clinical benefit of reducing the need for intubation. Although the SABA is useful for AE, it is not appropriate for maintenance therapy. Based on GINA guidelines, the use of as-needed SABA alone is currently no longer recommended for patients with mild asthma (2) because of the associated risk of severe exacerbation and even death (30, 37, 38). Maintenance therapy with controllers must be recommended to all patients with asthma regardless of the severity of their condition. Achieving good control of the asthma and preventing the future risk for exacerbation should be the primary concern.

One of the potential weaknesses of our study is that it is a unicentric retrospective study, the findings of which may not have external validity. For example, our database did not include information on previous clinical asthma control methods used within the past 12 months nor did it consider data on spirometry. In addition, the baseline characteristics, including smoking status and comorbidity, may be under-reported in the clinical charts. Another important consideration is that the precipitating factors of exacerbation were not clearly identified, and such missing information might have confounded the clinical or laboratory outcomes. Moreover, our study covered only two years, which may have been too short a period to gather enough data or to recruit a large enough group of patients to arrive at significant conclusions. Although our report identifies one independent clinical predictor, we believe that other factors found to be

insignificant in the multivariate analysis might carry a considerable risk of increasing the need for intubation in AE patients.

Despite these limitations, a history of 1-2 asthmatic exacerbations in the past 12 months has been demonstrated to be a significant clinical predictor of requiring intubation and IMV among patients hospitalized with AE-related conditions. In addition, being male and having a high level of blood eosinophils may increase the risk of requiring intubation, while taking any controller and/or SABA may decrease the risk of requiring intubation in AE-related hospitalization cases.

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Declaration of interest statement

The authors report no conflicts of interest.

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Table 1. Demographic characteristics of the study population

	Study Population (N=509)		Study Population (N=509)
Female (%)	367 (72.1)	GINA step treatment (%)	
Median age, years	53 (40, 65)	Step 1	241 (47.3)
Smoking status (%)		Step 2	17 (3.3)
Active smoker	55 (10.8)	Step 3	74 (14.5)
Former smoker	32 (6.3)	Step 4	156 (30.6)
Never smoker	245 (48.1)	Step 5	21 (4.1)
NA	177 (34.8)	Asthmatic exacerbation in previous 12 months (%)	
Smoking (pack-year)	10 (3.19, 23.3)	No previous attack	227 (44.6)
Previous clinic visited (%)		1-2 previous attacks	136 (26.7)
General medical clinic	203 (39.9)	>2 previous attacks	146 (28.7)
Asthma clinic	85 (16.7)	Median previous hospitalisation, time (IQR)	1 (0,3)
Family clinic	7 (1.4)	Intubation (%)	93 (18.3)
Rural hospital	57 (11.2)	Death (%)	13 (2.6)
Private clinic	8 (1.6)		
Never	149 (29.3)		
Comorbidities (%)			
Cardiovascular disease	51 (10)		
Chronic kidney disease	12 (2.4)		
Allergic rhinitis	49 (9.6)		
Diabetes Mellitus	80 (15.7)		
GERD	21 (4.1)		
Old pulmonary TB	9 (1.8)		

Values are shown as median (interquartile range, IQR) or number (%).

Abbreviations: NA, not available; GERD, gastroesophageal reflux; TB, tuberculosis; GINA,

Global Initiative for Asthma.

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Table 2. Characteristic and clinically relevant data between intubated and non-intubated patients

	Intubation (N=93)	Non intubation (N=416)	P-Value
Median age, years	48 (33.5, 71)	54 (42, 64)	0.415
Gender (%)			0.005
Male	37 (39.78)	105 (25.24)	
Female	56 (60.21)	311 (74.75)	
Comorbidities (%)			0.033
5 or more co-morbidities	0	15 (3.61)	
3-4 co-morbidities	8 (8.60)	33 (7.93)	
1-2 co-morbidities	26 (27.96)	162 (38.94)	
No co-morbidities	59 (63.44)	206 (49.52)	
Median Number of previous exacerbations within 12 months	2 (0, 1)	1 (0, 3)	<0.001
Controller (%)			<0.001
No	60 (64.5)	181 (43.5)	
Yes	33 (35.5)	235 (56.5)	
GINA step treatment (%)			0.005
Step 1	60 (64.5)	181 (43.5)	
Step 2	2 (2.2)	15 (3.6)	
Step 3	12 (12.9)	62 (14.9)	
Step 4	16 (17.2)	140 (33.7)	
Step 5	3 (3.2)	18 (4.3)	
Smoking status (%)			0.006
Active smoker	19 (20.4)	36 (8.7)	
Former	3 (3.2)	29 (7)	
Non smoker	39 (41.9)	206 (49.5)	

NA	32 (34.4)	145 (34.9)	
Vital signs			
Median temperature (°C)	37 (36.7, 37.5)	36.9 (36.6, 37.3)	0.031
Median SBP (mmHg)	131 (112, 156.5)	136 (120, 150)	0.168
Median DBP(mmHg)	80 (70, 92.5)	80 (70, 87)	0.111
Median pulse rate (bpm)	111 (100, 122)	102 (90, 114)	<0.001
Median RR (time/minute)	27 (22, 30)	24 (22, 26)	<0.001
Laboratory investigations			
WBC (cells/mm ³)	14,820 (11,625, 20,510)	10,355 (7,782, 13,020)	<0.001
ANC (cells/mm ³)	11,840 (7,750, 14,655)	8,144 (5,509, 11,043)	<0.001
Percentage of eosinophils	1 (0,3)	1 (0,3)	0.870
AEC (cells/mm ³)	121.3 (0, 593)	94.3 (0, 332)	0.160

Values are shown as median (interquartile range) or number (%).

Abbreviations: NA, not available; GINA, Global Initiative for Asthma; SP, systolic blood

pressure; DP, diastolic blood pressure; RR, respiratory rate; WBC, white blood cells;

ANC, absolute neutrophil count; AEC, absolute eosinophil count.

Table 3. Clinical outcomes of asthmatic exacerbation-related hospitalizations

Clinical outcomes	Intubation (N=93)	Non-intubation (N=416)	P-value
Median length of stay, days	4 (3, 7.5)	2 (1,4)	<0.001
Shock, n (%)	19 (20.43)	0	<0.001
Death, n (%)	13(13.9)	0	<0.001
Complication, n (%)			<0.001
Pneumonia	20 (21.50)	12 (2.88)	
Heart failure	0	2 (0.48)	
Tracheostomy	4 (4.30)	1 (0.24)	
No complications	69 (74.19)	401 (96.39)	
Total Systemic steroids used			
Median prednisolone equivalent dose (mg)	175 (100, 300)	87.5 (40,150)	<0.001

Values are shown as median (interquartile range) or number (%).

Table 4. Univariate logistic regression analysis for intubation in asthmatic exacerbation-related hospitalizations

Clinical predictors	Comparison	OR	95% CI	P-value
Univariate analysis				
Gender	Male vs Female	1.96	1.22-3.13	0.005
Age (Years)		1.00	0.99-1.02	0.636
Smoking status	Yes vs No	0.56	0.31-1.01	0.055
SABA	Yes vs No	0.36	0.23-0.57	<0.001
Controller	Yes vs No	0.42	0.27-0.68	<0.001
GINA step treatment	1 vs 5	0.50	0.14-1.77	0.284
	2 vs 5	1.25	1.84-8.49	0.819
	3 vs 5	0.86	0.22-3.39	0.831
	4 vs 5	1.46	0.39-5.50	0.577
Asthmatic exacerbations in the past 12 months	>2 vs Never	2.85	1.59-5.11	<0.001
	1-2 vs Never	3.27	1.75-6.12	<0.001
Number of asthmatic exacerbations in the past 12 months		1.19	1.07-1.34	0.002
Absolute eosinophil count (cells/mm ³)		1.00	0.99-1.00	0.159
Absolute neutrophil count (cells/mm ³)		1.00	0.98-1.01	0.138
Level of absolute eosinophil count (cells/mm ³)	≥300 vs <300	1.68	1.05-2.69	0.031

Abbreviations: CI, confidence interval; OR, odds ratio; SABA, short acting beta2 agonist.

Table 5. Multivariate logistic regression analysis for factors increasing risk of intubation in asthmatic exacerbation-related hospitalizations

Clinical predictors	Comparison	OR	95% CI	P-value
Multivariate analysis				
Gender	Male vs Female	0.61	0.27-1.37	0.231
Smoking status	Yes vs No	0.77	0.32-1.81	0.547
SABA	Yes vs No	1.56	0.68-3.53	0.292
Controller	Yes vs No	1.08	0.45-0.62	0.859
Asthmatic exacerbations in the past 12 months	1-2 vs Never	3.12	1.19-8.21	0.021
	>2 vs Never	2.05	0.44-9.58	0.362
Number of asthmatic exacerbations in the past 12 months		1.06	0.84-1.35	0.616
Level of absolute eosinophil count (cells/mm ³)	≥300 vs <300	0.55	0.29-1.04	0.065

Abbreviations: CI, confidence interval; OR, odds ratio; SABA, short acting beta2 agonist